Articles

Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58 209 women with breast cancer and 101 986 women without the disease

*Collaborative Group on Hormonal Factors in Breast Cancer**

Summary

Background Women with a family history of breast cancer are at increased risk of the disease, but no study has been large enough to characterise reliably how, over women's lives, this risk is influenced by particular familial patterns of breast cancer. This report, on the relevance of breast cancer in first-degree relatives, is based on combined data from 52 epidemiological studies.

Methods Individual data on breast cancer in first-degree relatives (mothers, sisters, and daughters) of 58 209 women with breast cancer and of 101 986 controls were collected, checked, and analysed centrally. Risk ratios for breast cancer were calculated by conditional logistic regression, stratified by study, age, menopausal status, number of sisters, parity, and age when the first child was born. Breast-cancer incidence and mortality rates for particular family histories were calculated by applying age-specific risk ratios to breast-cancer rates typical for more-developed countries.

Findings Altogether 7496 (12·9%) women with breast cancer and 7438 (7·3%) controls reported that one or more first-degree relatives had a history of breast cancer: 12% of women with breast cancer had one affected relative and 1% had two or more. Risk ratios for breast cancer increased with increasing numbers of affected first-degree relatives: compared with women who had no affected relative, the ratios were 1·80 (99% CI 1·69–1·91), 2·93 (2·36–3·64), and 3·90 (2·03–7·49), respectively, for one, two, and three or more affected first-degree relatives (p<0·0001 each). The risk ratios were greatest at young ages, and for women of a given age, were greater the younger the relative was when diagnosed. The results did not differ substantially between women reporting an affected mother (9104) or sister (6386). Other factors, such as childbearing history, did not significantly alter the risk ratios associated with a family history of breast cancer. For women in more-developed countries with zero, one, or two affected first-degree relatives, the estimated cumulative incidence of breast cancer up to age 50 was 1·7%, 3·7%, and 8·0%, respectively; corresponding estimates for incidence up to age 80 were 7·8%, 13·3%, and 21·1%. Corresponding estimates for death from breast cancer up to age 80 were 2·3%, 4·2%, and 7·6%. The age when the relative was diagnosed had only a moderate effect on these estimates.

Interpretation Eight out of nine women who develop breast cancer do not have an affected mother, sister, or daughter. Although women who have first-degree relatives with a history of breast cancer are at increased risk of the disease, most will never develop breast cancer, and most who do will be aged over 50 when their cancer is diagnosed. In countries where breast cancer is common, the lifetime excess incidence of breast cancer is 5·5% for women with one affected first-degree relative and 13·3% for women with two.

Lancet 2001; **358:** 1389–99

Introduction

A woman's risk of developing breast cancer is increased if she has a family history of the disease. However, no study has been large enough to characterise reliably how, over a woman's life, the risk of breast cancer is influenced by particular patterns of disease in first-degree relatives (mothers, sisters, or daughters). The Collaborative Group on Hormonal Factors in Breast Cancer has brought together, for central review and analysis, relevant data from 52 epidemiological studies of women with breast cancer. Findings from these studies have already been published on the relation between breast cancer and the use of hormonal contraceptives and of hormone replacement therapy.[1–3] This report, which presents data on 58 209 women with breast cancer and 101 986 controls, describes the relevance of the pattern of breast cancer in first-degree female relatives to a woman's risk of developing the disease at various ages. Although estimates of absolute risk would depend on breast-cancer incidence rates, genetic background, and childbearing history in each population studied, the patterns reported here may be expected to have general application.

Methods

Contributing studies and collection of data

Epidemiological studies were eligible for this collaboration if they included at least 100 women with incident invasive breast cancer and sought information from each woman on reproductive and hormonal factors. Methods for identifying such studies have been described elsewhere, and we estimate that more than 80% of eligible data worldwide are included in this collaboration.[1–3] Data sought from principal investigators of each study included whether or not each woman's mother, sister(s), or daughter(s) had been diagnosed as having breast cancer, and, if so, the age of that relative at diagnosis of breast cancer. Details were also sought on the numbers of sisters and daughters that each woman had and the ages of each first-degree female relative. Cohort studies were included using a nested case-control design, in which four controls were selected at random, matched on follow-up to the age-at-diagnosis of the case and, where approporiate,

*Collaborators and collaborating centres are given on *The Lancet's* website (www.thelancet.com)

Correspondence to: ICRF Cancer Epidemiology Unit, Gibson Building, Radcliffe Infirmary, Oxford OX2 6HE, UK

Study (country)	Cases					Controls				
	Total	Median age (years)	Mean number of sisters	Number with a mother with breast cancer	Number with one or more sisters with breast cancer	Total	Median age (years)	Mean number of sisters	Number with a mother with breast cancer	Number with one or more sisters with breast cancer
Cohort studies										
Alexander (Scotland)[10]	186	56	NA	8	12	743	56	NA	37	15
Schairer (USA)[39]	1032	61	1·52	126	98	4097	61	1·63	327	326
Nurses Health Study (USA)[15]	2870	53	1·30	274	105	11 480	53	1·30	579	219
Canadian NBSS (Canada)[28]	1339	53	NA	154	94	5327	53	NA	449	285
American Cancer Society (USA)[33]	1270	64	1·20	93	38	5075	64	1·32	187	110
Netherlands Cohort (Netherlands)[45]	471	64	2·54	28	37	1690	63	2.51	52	90
Iowa Women's Health (USA)[30]	1188	67	2·33	44	33	4752	67	2·39	131	158
Million Women Study (UK)[53]	1074	56	1·10	94	48	4296	56	1·16	271	137
Case control studies with population controls										
Brinton (USA)[17]	3217	54	1·54	405	398	3545	54	1·60	256	217
Nomura (Hawaii)[8]	315	57	2·11	11	24	315	58	2·05	9	8
Hislop (Canada)[6]	949	53	NA	80	67	949	52	NA	44	30
CASH (USA)[26]	4457	46	1·53	379	160	4676	46	1·57	203	82
UK National (UK)[18]	755	33	1·20	64	10	755	33	1·11	28	4
Bain/Siskind (Australia)[16]	487	56	2·01	29	32	981	56	1·98	31	29
Rohan (Australia)[13]	451	57	1·62	25	21	451	57	1·52	14	13
Rosero-Bixby (Costa Rica)[11]	171	46	3·31	6	5	826	38	3·40	14	18
Meirik/Lund (Norway/Sweden)[7]	422	38	1·06	40	6	527	37	1·04	22	2
Long Island Study (USA)[25]	1184	57	1·45	113	86	1184	57	1·37	59	64
Clarke (Canada)[29]	607	52	1·64	40	40	1213	52	1·52	48	34
Yuan/Yu (China)[14]	534	52	NA	11	0	534	51	NA	4	0
Wang/Yu (China)[31]	300	45	1·81	5	2	300	45	1·89	1	0
Paul-Skegg (New Zealand)[20]	891	46	1·54	65	41	1864	41	1·59	62	26
Daling (USA)[40]	747	38	1·18	98	27	961	36	1·26	45	7
4 State Study (USA)[36]	6888	61	1·72	622	678	9529	59	1·72	568	523
Rookus/van Leeuwen (Netherlands)[38]	918	42	1·84	75	44	918	42	1·91	35	25
CRC/ICRF (England) unpublished	644	42	0·99	57	18	644	42	0·97	41	3
Sanjose (Spain)[48]	330	58	1·25	20	14	346	60	1·47	6	6
Yang/Gallagher (Canada)[32]	1019	58	NA	104	92	1025	58	NA	57	47
Primic/Zakelj (Slovenia)[44]	619	46	NA	35	23	619	46	NA	25	6
Stanford/Habel (USA)[47]	450	57	1·21	46	30	492	57	1·26	41	26
ICRF (England) unpublished	472	50	0·98	45	17	472	50	1·06	30	12
WISH (USA)[41]	1866	41	1·55	216	56	2009	41	1·64	108	27
McCredie/Hopper 1 (Australia)[49]	466	36	1.35	46	15	408	35	1·36	19	1
Magnusson (Sweden)[52]	3169	62	1·33	284	235	3363	63	1·40	152	111
McCredie/Hopper 2 (Australia)[51]	1020	43	1·27	104	38	131	35	1·24	2	0
Case control studies with hospital controls										
Vessey 1 (UK)[4]	1269	42	1·36	112	35	1271	42	1·58	64	19
Modan (Israel)[9]	1065	56	1·80	27	32	1945	56	1·81	22	19
Hulka 1 (USA)[21]	279	57	1·95	15	15	2117	51	2·29	44	60
Kalache (Brazil)[34]	579	49	3·53	6	23	808	50	3·61	4	2
Ravnihar (Slovenia)[12]	531	46	1·80	18	17	1939	46	1·83	38	19
Vessey 2 (UK)[19]	1125	49	1·30	79	41	1125	49	1·35	50	19
Lê (France)[5]	265	39	1·37	15	7	265	39	1·42	8	4
Gerber (France)[24]	444	53	1·26	19	9	563	50	1·38	10	4
Clavel (France)[22]	495	45	1·41	31	19	896	44	1·38	44	10
La Vecchia (Italy)[35]	3263	52	1·53	205	160	2729	53	1·67	60	63
Lee (Singapore)[27]	200	50	NA	4	7	420	50	NA	3	3
Lacaya/Ngelangel (Philippines)[37]	283	46	3·34	5	10	283	43	3·29	2	9
Katsouyanni (Greece)[43]	795	56	1·74	25	20	1548	55	1·82	40	40
Franceschi (Italy)[42]	2569	55	1·52	133	134	2588	56	1·76	60	66
Hamajima (Japan)[50]	1483	49	1·53	38	72	5925	49	1·47	80	110
Levi (Switzerland)[46]	257	55	NA	19	15	538	57	NA	13	15
Gajalakshmi (India)[23]	529	50	NA	8	3	529	49	NA	0	0
Total	58 209*	52	1·52	4605	3263	101 986*	53	1·59	4499	3123

NA = not available. *Includes 55 cases and 79 controls with breast cancer in at least one daughter.

Table 1: **Details of studies included in these analyses**

broad geographical region. All data were checked centrally and apparent inconsistencies or implausibilities were corrected by correspondence with the appropriate investigator.

The 52 studies included in these analyses[4–53] (and two unpublished studies) are those that contributed information on breast cancer in mothers and sisters; 17 of them also contributed information on breast cancer in daughters.[6,8,13,17,21,23,25,26,28,30–32,34,39,42,47,48] Data on breast cancer in mothers, sisters, and daughters were combined for most analyses, and 'number of first-degree relatives with breast cancer' refers to the total number reported to have had the disease at the time that enquiries were made. Few studies had collected information on the ages of unaffected first-degree relatives and this information was not incorporated into these analyses.

Statistical analysis and presentation of results

Risk ratios were estimated by conditional logistic regression (Stata Statistical Software, release 5.0). To ensure that women in one study were compared only with similar women in the same study, analyses were routinely stratified

Number of first-degree relatives* with breast cancer	Cases (n=58 209)	Controls (n=101 986)	Risk ratio (99% FCI)†
None	50 713	94 548	1·00 (0·97–1·03)
1	6810	6998	1·80 (1·70–1·91)
2	603	404	2·93 (2·37–3·63)
3 or more	83	36	3·90 (2·03–7·49)

*Mother, sister or daughter. †Risk ratios are calculated as floating absolute risks (FAR), with FAR=1·0 for women with no affected relative (see methods). All analyses are stratified by study, age at diagnosis, menopausal status, number of sisters, parity and age at first birth.

Table 2: **Risk ratios for breast cancer, by number of first-degree relatives with a history of breast cancer**

by study, by centre within study, by fine divisions of age at diagnosis or pseudodiagnosis (16–19, 20–24, 25–29, by single years from 30–79, 80–84, and 84–89), by menopausal status (premenopausal, less than 5 years since menopause, 5 or more years since menopause, hysterectomy, unknown), by number of sisters (none, one, two or more, unknown), and by parity and age at first birth. Nulliparous women were assigned to a separate stratum, and parous women were cross-classified according to their parity (one or two, three or four, five or more) and their age when their first child was born (younger than 20 years, 20–29 years, 30 years and older). The number of cases and controls quoted in each table or figure is the total in each respective category.

When two groups were compared, conventional risk ratios and their 99% CI are quoted. In analyses involving comparison of more than two groups, risk ratios are described as floating absolute risks[54] (FAR), with corresponding 99% floated CI (FCI); this approach does not alter the value of the risk ratio, but slightly reduces the variances attributed to those risk ratios that are not defined as 1·0. Any comparison between two groups must take the variation in both FARs into account (by summing the variances of the logarithms of the two FARs).

Heterogeneity and, where appropriate, trends were assessed by χ^2 tests (which take into account the variances of all the FARs). Graphically, risk ratios or FARs are represented as black squares, with areas inversely proportional to the variance of the log of the risk ratio or FAR, indicating the amount of statistical information available for that particular estimate. The corresponding CI or FCI is drawn as a line, and this is indicated by an arrow if the line extends beyond the scale of the plot.

Estimated incidence of and mortality from breast cancer

To translate estimates of the proportional increase in risk at various ages into absolute rates at those ages, we used age-specific mortality rates for breast cancer in more-developed countries in 1990[55] and age-specific incidence rates typical of those countries at a similar time.[2,3] First, the age-specific incidence of breast cancer over a 10-year period was calculated, according to the number of affected relatives. The probability of developing breast cancer from age 20 to age 50 and to age 80 was then estimated for women who, at a given age, are free from breast cancer and who have a given number of affected relatives at that age. In each calculation account was taken of the fact that, as the population ages, additional relatives will be diagnosed with breast cancer; the transition probability that a relative will be diagnosed with breast cancer in each 5-year period was estimated from the number of first-degree female relatives, the number of such relatives with a history of breast cancer and their estimated incidence of breast cancer. Account was also taken of the fact that, as women age, the number at risk of breast cancer is diminished over time by those with previously diagnosed breast cancer and by those who have already died from other causes. Estimates of the absolute risks of mortality from breast cancer were also made using a similiar approach but assuming that the risk ratios for death from breast cancer at a particular age correspond to those for breast cancer incidence 10 years earlier.

Woman's age (years)	With an affected relative Cases/controls	Without an affected relative Cases/controls	Risk ratio* (99% CI)
One affected relative			
<35	323/197	3356/6094	2·91 (2·05–4·13)
35–39	518/330	4595/6775	2·53 (1·97–3·23)
40–44	843/557	6693/10 354	2·13 (1·76–2·57)
45–49	927/871	7430/12 735	1·84 (1·55–2·17)
50–54	1198/1176	8377/15 513	1·99 (1·71–2·32)
55–59	862/1230	6023/13 084	1·53 (1·29–1·80)
60–64	870/1108	5882/12 636	1·46 (1·23–1·74)
65–69	697/863	4745/9733	1·61 (1·37–1·89)
⩾70	572/666	3612/7624	1·64 (1·36–1·99)
Two affected relatives			
<45	33/111	14 644/23 223	5·26 (2·58–10·73)
45–54	110/165	15 807/28 248	3·17 (2·03–4·96)
55–64	134/171	11 905/25 720	2·67 (1·76–4·07)
⩾65	127/156	83 75/17 339	2·28 (1·59–3·29)

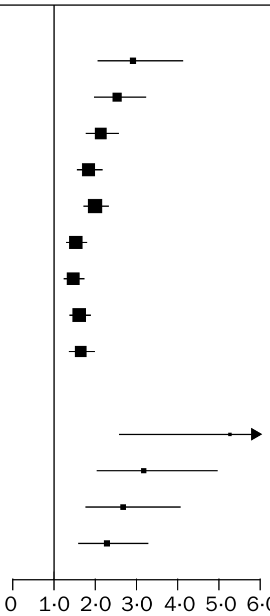


Figure 1: **Age-specific risk ratios for breast cancer in relation to history of breast cancer in first-degree relatives**
*Relative to a woman with no affected relative, stratified by study, age at diagnosis, parity, age at first birth, menopausal status, and number of sisters.

Woman's age (years)	Relative's age at diagnosis of breast cancer								No relative with breast cancer	
	<40 years		40–49 years		50–59 years		⩾60 years		Cases/ controls	Risk ratio* (99% FCI)
	Cases/ controls	Risk ratio* (99% FCI)	Cases/ controls	Risk ratio* (99% FCI)	Cases/ controls	Risk ratio* (99% FCI)	Cases/ controls	Risk ratio* (99% FCI)		
<40	125/41	5·7 (2·7–11·8)	173/95	2·9 (1·9–4·4)	150/87	2·8 (1·7–4·5)	113/96	2·0 (1·2–3·2)	4828/7767	1·0 (0·94–1·06)
40–49	132/76	3·0 (1·8–4·9)	304/196	2·0 (1·5–2·8)	291/199	2·3 (1·7–3·2)	431/378	1·7 (1·3–2·1)	8678/13448	1·0 (0·95–1·05)
50–59	94/107	2·0 (1·2–3·4)	251/257	2·2 (1·6–3·0)	286/322	1·6 (1·2–2·1)	571/707	1·6 (1·3–2·0)	8368/17532	1·0 (0·95–1·05)
⩾60	87/122	1·4 (0·9–2·1)	181/241	1·4 (1·0–2·0)	245/330	1·5 (1·2–2·0)	641/774	1·4 (1·2–1·7)	6949/15195	1·0 (0·95–1·06)

See footnote to table 2.

Table 3: **Age-specific risk ratios for breast cancer in women with one first-degree relative with a history of the disease, according to the relative's age at diagnosis of breast cancer**

Results

Overall findings

Altogether 58 209 women with invasive breast cancer (cases) and 101 986 women without breast cancer (controls) from 52 studies were included in these analyses (table 1). The median age of the women varied substantially from one study to another, but for all studies combined it was 52 for cases and 53 for controls. The proportion of women reporting a history of breast cancer in a mother or sister also varied from one study to another, tending to increase as the median age of the study population increased. Overall, 7496 (12·9%) cases and 7438 (7·3%) controls reported that at least one first-degree relative had a history of breast cancer; the disease was reported in the mothers of 9104, the sisters of 6386, and the daughters of 134 women. Women with breast cancer reported fewer children than controls (2·23 *vs* 2·50, p<0·0001) and also slightly fewer sisters (1·52 *vs* 1·59, p<0·0001).

Table 2 shows the numbers of cases and controls who reported first-degree relatives with a history of breast cancer, together with the corresponding risk ratios. The risk ratios increased with increasing number of affected relatives (p<0·0001 for each comparison against women with no such relative): compared with women who had no affected relative, the risk ratios associated with one, two, and three or more affected relatives were 1·80 (99% CI 1·69–1·91), 2·93 (2·36–3·64), and 3·90 (2·03–7·49). Only 83 (0·14%) cases and 36 (0·04%) controls reported that three or more first-degree relatives had a history of breast cancer, and most subsequent analyses do not present results separately for this small group.

The risk ratio for breast cancer associated with a family history of the disease decreased with age, at least up to about age 60. Figure 1 shows age-specific risk ratios for breast cancer for women with one affected first-degree relative (χ^2_1 for trend with age 37·1, p<0·0001) and for women with two affected relatives (χ^2_1 for trend 7·0, p=0·008). For women younger than 50 years and 50 and older, respectively, the risk ratios compared with women who had no affected relatives were 2·14 (1·92–2·38) and 1·65 (1·53–1·78) with one affected relative, 3·84 (2·37–6·22) and 2·61 (2·03–3·34) with two affected relatives, and 12·05 (1·70–85·16) and 2·65 (1·29–5·46) with three or more affected relatives.

The results in figure 1 were examined in detail to assess whether adjustments for other possible confounders such as race, age at menarche, education, height, weight, or use of oral contraceptives or hormone-replacement therapy modified the magnitudes of the risk ratios; none was found to have a material effect on the results. The age-specific results were also examined further according to study design. The respective risk ratios associated with one affected relative for cohort studies, case-control studies with population controls, and case-control studies with hospital controls were 2·04 (1·72–2·69), 2·19 (1·95–2·47), and 1·86 (1·45–2·37) for women younger than 50 years, and 1·50 (1·32–1·71), 1·64 (1·47–1·82), and 2·22 (1·77–2·84) for women aged 50 years and older.

Dual effect of the woman's and her relative's age

Information on the age of each affected first-degree relative at the time that her breast cancer was diagnosed was provided in 27 studies[7,11,14–17,19,20,22,26,29,31–33,36,39–41,44,46–49,51,53] (and two unpublished studies) representing 57% of the women included in these analyses. Risk ratios according to the ages of both the women and their relatives are given in tables 3 and 4. Among women of a given age, the risk ratios associated with a family history of breast cancer tended to be greater the younger the relatives were when their breast cancer was diagnosed, especially for women younger than 50 years.

The results in table 3 did not vary substantially according to whether the affected relative was a mother or a sister, after allowance for the woman's and relative's ages. For example, in women younger than 50 years, the risk ratio associated with having one relative diagnosed with breast cancer before age 50 was 2·41 (1·86–3·12) for an affected mother and 3·18 (2·15–4·72) for an affected sister. Few women younger than 50 reported that they had a sister who was diagnosed with breast cancer after age 50 (83 cases and 43 controls). For women aged 50 or older, the risk ratios associated with having one relative who was diagnosed with breast cancer before age 50 were 1·89 (1·41–2·53) for an affected mother and 1·66 (1·28–2·16) for an affected sister; and the corresponding risk ratios for breast cancer diagnosed in one relative who was 50 or older at diagnosis were 1·60 (1·38–1·84) for an affected mother and 1·44 (1·19–1·73) for an affected sister. The number of sisters a

Woman's age (years)	At least one relative diagnosed before age 40		Both relatives diagnosed after age 40		No relative with breast cancer	
	Cases/ controls	Risk ratio (99% FCI)	Cases/ controls	Risk ratio (99% FCI)	Cases/ controls	Risk ratio (99% FCI)
<50	60/11	13·5 (3·4–53·9)	56/12	7·8 (2·4–25·0)	13 506/21 215	1·0 (0·9–1·1)
⩾50	54/25	3·9 (1·8–8·6)	200/150	2·6 (1·8–3·7)	15 317/32 727	1·0 (0·9–1·1)

*See footnote to table 2.

Table 4: **Age-specific risk ratios for breast cancer in women with two first-degree relatives with a history of the disease, according to the relatives' ages at diagnosis of breast cancer**

Characteristic	Cases/controls	Risk ratio* (99% FCI)
Parity		
Nulliparous	1194/937	1·00 (0·86–1·16)
One	1116/824	0·99 (0·85–1·16)
Two	2300/2119	0·80 (0·72–0·89)
Three	1544/1720	0·74 (0·66–0·83)
Four or more	1321/1792	0·66 (0·58–0·75)
Age when first child was born		
<20	731/721	0·72 (0·60–0·87)
20–24	2592/2877	0·73 (0·66–0·80)
25–29	1965/2038	0·78 (0·70–0·87)
⩾30	976/799	0·93 (0·79–1·09)
Nulliparous	1194/937	1·00 (0·86–1·16)
Menopausal status		
Premenopausal	2632/1756	1·00 (0·68–1·47)
Postmenopausal		
<45 at menopause	696/979	0·63 (0·51–0·78)
45–49 at menopause	838/972	0·83 (0·68–1·01)
⩾50 at menopause	1790/1925	0·96 (0·82–1·12)
Use of oral contraceptives		
Never	4434/4410	1·00 (0·83–1·21)
Last use <10 years ago	969/640	0·77 (0·54–1·11)
Last use ⩾10 years ago	1354/1362	1·01 (0·80–1·28)
Use of hormone replacement therapy		
Never	1909/2015	1·00 (0·84–1·19)
Last use <5 years ago	453/579	1·18 (0·84–1·66)
Last use ⩾5 years ago	262/347	1·20 (0·83–1·75)

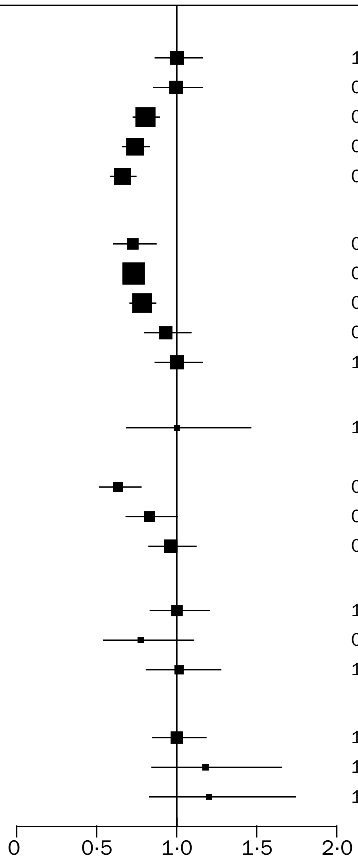


Figure 2: **Risk ratios for breast cancer according to various factors among women who had one or more first-degree relatives with a history of breast cancer**
Risk ratios calculated as FAR (see methods). Stratified by study, age at diagnosis, number of sisters, and where appropriate parity, age at first birth, and menopausal status.

woman had did not substantially alter the results; for women with zero, one, two, or three or more sisters, the risk ratios associated with having one affected relative were 1·82 (1·59–2·08), 2·01 (1·78–2·26), 1·79 (1·53–2·10), and 1·71 (1·49–1·97). There were too few women with affected daughters (55 cases and 79 controls) for reliable estimates of risk to be made.

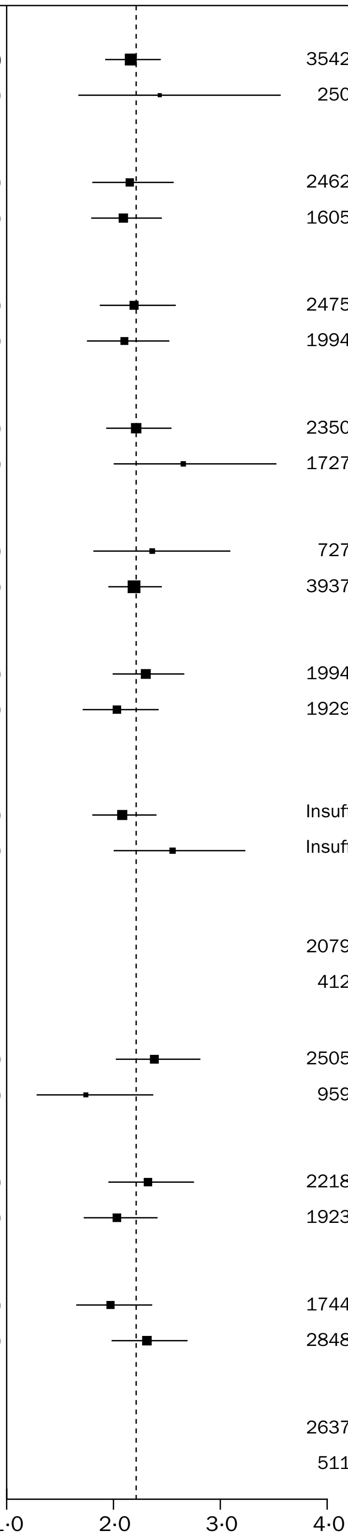
Role of other factors

Figure 2 shows analyses, restricted to women with one or more affected first-degree relatives, of the risk ratio for breast cancer associated with various factors, including a woman's parity, her age when her first child was born, and her use of hormonal therapies. The relations shown in figure 2 for women with a family history of breast cancer were similar to those seen for women without such a history (see web figure 1 on *The Lancet*'s website: www.thelancet.com), although some of the CIs were wide for women with a family history, especially those associated with the use of hormonal therapies. Figure 3 shows the results of formal tests for interaction between having an affected first-degree relative and various factors with respect to the relative risk of breast cancer. Overall tests for heterogeneity were calculated by summing the respective individual χ^2 values to give a global χ^2 statistic of χ^2_{10}=19·2 (p=0·04) for age under 50 years and χ^2_{11}=15·1 (p=0·2) for women aged 50 years and older. Of the 21 comparisons shown in figure 3, the most extreme differences were those according to the amount of alcohol drunk each week. However, the results for women younger than 50 years were in the opposite direction to those for women older than 50, which suggests that any apparent differences might be largely or wholly due to chance. Further subdivision of the results shown in figure 3 for women younger than 50 according to the age of their affected relative gave global χ^2 values for interaction of χ^2_{10}=9·1 (p=0·5) for women whose relative was younger than 50 and χ^2_{10}=6·8 (p=0·7) for women whose relative was 50 or older (see web figure 2 on *The Lancet*'s website: www.thelancet.com). A subgroup of particular interest is women younger than 50 whose affected relative was also younger than 50 at diagnosis in relation to use of oral contraceptives; in these women the risk ratio associated with having an affected relative younger than 50 was 3·85 (2·41–6·13) for women who had used oral contraceptives in the previous 10 years and 2·91 (2·15–3·93) for women who had not (χ^2_1 for interaction=1·7, p=0·2).

Tumour spread

Among women with breast cancer, having an affected first-degree relative did not appear to influence the extent of the spread of the tumour. Compared with women with no affected first-degree relative, the relative probability of having a tumour that had spread beyond the breast compared with a localised tumour was 0·96 (0·83–1·12) for women with one affected relative and 0·85 (0·54–1·35) for women with two affected relatives.

Characteristic	Women aged <50 years: Cases/controls with affected relatives	Women aged <50 years: Risk ratio (99% CI)	Women aged ⩾50 years: Cases/controls with affected relatives	Women aged ⩾50 years: Risk ratio (99% CI)
Race				
White	2119/1564	2·16 (1·92–2·44)	3542/4038	1·64 (1·51–1·78)
Other	254/232	2·43 (1·67–3·56)	250/354	2·11 (1·43–3·11)
Education				
<13 years	1238/820	2·15 (1·80–2·56)	2462/2669	1·76 (1·58–1·96)
⩾13 years	1433/1059	2·09 (1·79–2·45)	1605/2285	1·71 (1·51–1·94)
Height				
<165 cm	1403/959	2·19 (1·87–2·58)	2475/2771	1·79 (1·60–1·99)
⩾165 cm	1314/857	2·10 (1·75–2·52)	1994/2038	1·67 (1·47–1·90)
Body mass index				
<25·0 kg/m²	1838/1233	2·21 (1·93–2·54)	2350/2803	1·77 (1·58–1·97)
⩾25·0 kg/m²	671/474	2·65 (2·00–3·52)	1727/1790	1·73 (1·50–1·99)
Parity				
Nulliparous	467/256	2·36 (1·81–3·09)	727/681	1·72 (1·43–2·07)
Parous	2344/1767	2·19 (1·95–2·45)	3937/4688	1·72 (1·59–1·86)
Age at first birth				
<25 years	1329/1052	2·30 (1·99–2·66)	1994/2546	1·74 (1·56–1·95)
⩾25 years	1012/709	2·03 (1·71–2·42)	1929/2128	1·69 (1·51–1·89)
Use of oral contraceptives in previous 10 years				
No	1653/1222	2·08 (1·80–2·40)	Insufficient data	
Yes	807/469	2·55 (2·00–3·23)	Insufficient data	
Use of hormone replacement therapy in previous 5 years				
No	Insufficient data		2079/2279	1·83 (1·64–2·04)
Yes	Insufficient data		412/519	1·52 (1·10–2·09)
Alcohol				
<50 g/week	1351/921	2·38 (2·02–2·81)	2505/2733	1·68 (1·52–1·87)
⩾50 g/week	583/341	1·74 (1·28–2·37)	959/773	2·14 (1·72–2·68)
Smoking				
Never	1234/938	2·32 (1·95–2·75)	2218/2521	1·75 (1·57–1·96)
Ever	1331/939	2·03 (1·72–2·41)	1923/2014	1·77 (1·56–2·02)
Age at menarche				
<13 years	1262/875	1·97 (1·65–2·36)	1744/1974	1·73 (1·50–1·99)
⩾13 years	1541/1150	2·31 (1·98–2·69)	2848/3359	1·70 (1·54–1·87)
Type of menopause				
Natural	Insufficient data		2637/3047	1·72 (1·57–1·89)
Oopho-rectomy	Insufficient data		511/654	1·63 (1·24–2·15)



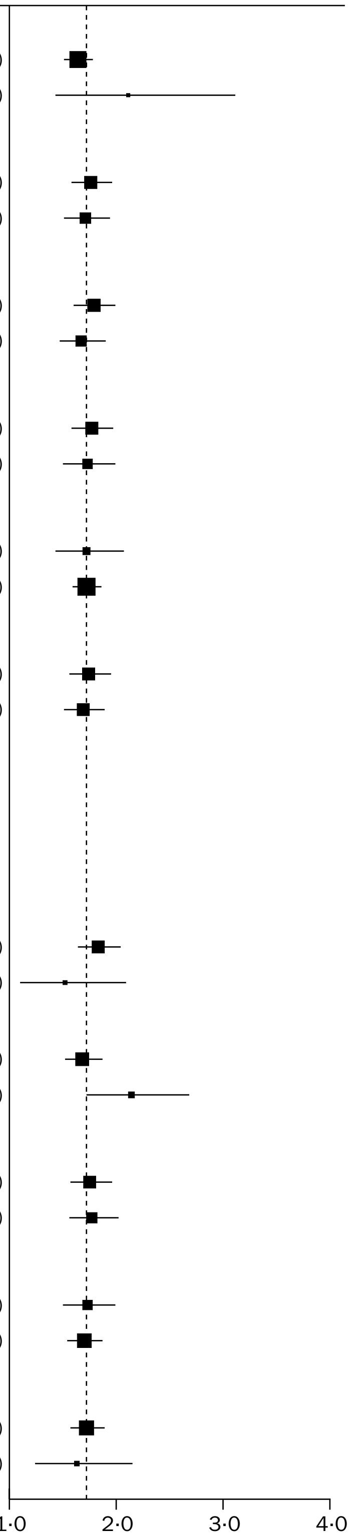


Figure 3: **Age-specific risk ratios* for breast cancer associated with having one or more affected first-degree relatives for women with differing characteristics**

*Relative to a woman with no affected relative, stratified by study, age at diagnosis, parity, age at first birth, menopausal status, and number of sisters. Dotted lines represent overall age-specific risk ratios for breast cancer in women with one or more affected relatives.

	Number of first-degree relatives now affected		
	Two	One	None
Probability (%) of developing breast cancer over the next 10 years			
20	0·2	0·1	0·04
30	2·0	1·0	0·4
40	5·2	2·5	1·4
50	5·3	3·2	1·9
60	5·6	3·5	2·3
70	5·7	4·2	2·5

Table 5: **Probability (%) that women in more-developed countries who are free from breast cancer at certain ages would develop breast cancer over the next 10 years, according to the number of affected relatives**

Incidence of breast cancer

Table 5 shows estimates of the number of breast cancers that would be diagnosed in 100 women from more-developed countries over a 10-year period for each decade of age, from 20 to 79, according to the number of affected first-degree relatives. Incidence increases with age, and breast cancer is uncommon before age 40, even for women with two affected relatives.

Estimates of the probability of developing breast cancer up to age 50 and to age 80, respectively, are also shown in table 6 for women who, at a particular age, are free from breast cancer and have a certain family history of the disease. The estimates take into account the fact that a small proportion of women in each family history category would change to another category if, at a future date, a relative was diagnosed with breast cancer. The estimated probability that a woman aged 20 would develop breast cancer by age 50 is 1·7%, 3·7%, and 8·0%, respectively, for women with zero, one, and two affected first-degree relatives. Corresponding estimates of the lifetime probability of developing breast cancers ie, incidences from age 20 to age 80, are 7·8%, 13·3%, and 21·1%, respectively. The lifetime excess probability of breast cancer is thus 5·5% for one and 13·3% for two affected relatives. Most breast cancers in women with a family history of the disease are likely to occur after age 50, even for women with two affected relatives. This can be seen in figure 4, which shows the estimated probability of developing breast cancer, by age, for women with various categories of family history at age 20; the excess lifetime probabilty of breast cancer after age 50 being 3·7% for one and 8·6% for two affected relatives.

Few women (83 cases and 36 controls) reported that they had three or more affected first-degree relatives, so the results for them are not as reliable as for women with exactly one or exactly two affected relatives. Nevertheless, application of the age-specific risk ratios calculated from these data provides estimates of cumulative probability of breast cancer of 19% by age 50 and 31% by age 80 for women with three or more affected first-degree relatives.

The risk ratios for breast cancer tended to be greater the younger the relatives were when their breast cancer was diagnosed, particularly among women who were themselves young (tables 3 and 4). Results from table 3 were used to re-estimate the probability of breast cancer for women with one affected relative, according to the relative's age at diagnosis of cancer. As expected, the estimated cumulative probability of breast cancer was greater the younger the relative was at diagnosis but, because the risk ratios differed substantially only at young ages when breast cancer is less common, the absolute excess was not large. For example, for women with one affected relative, estimates of cumulative probability of

Woman's age now (years)	Number of first-degree relatives now affected*		
	Two	One	None
Probability (%) of developing breast cancer by age 50			
20	8·0	3·7	1·7
30	7·4	3·5	1·7
40	5·2	2·5	1·3
Probability (%) of developing breast cancer by age 80			
20	21·1	13·3	7·8
30	20·7	13·0	7·7
40	18·9	12·0	7·3
50	14·7	9·8	6·1
60	10·4	7·1	4·5
70	5·7	4·2	2·5

*These estimates assume that, as the women age, an appropriate proportion of their relatives will be diagnosed with breast cancer and that the population at risk will be diminished by those who develop breast cancer or die (see methods).

Table 6: **Probability (%) that women in more-developed countries who are free from breast cancer at certain ages would develop breast cancer by age 50 and by age 80, according to the number of affected relatives**

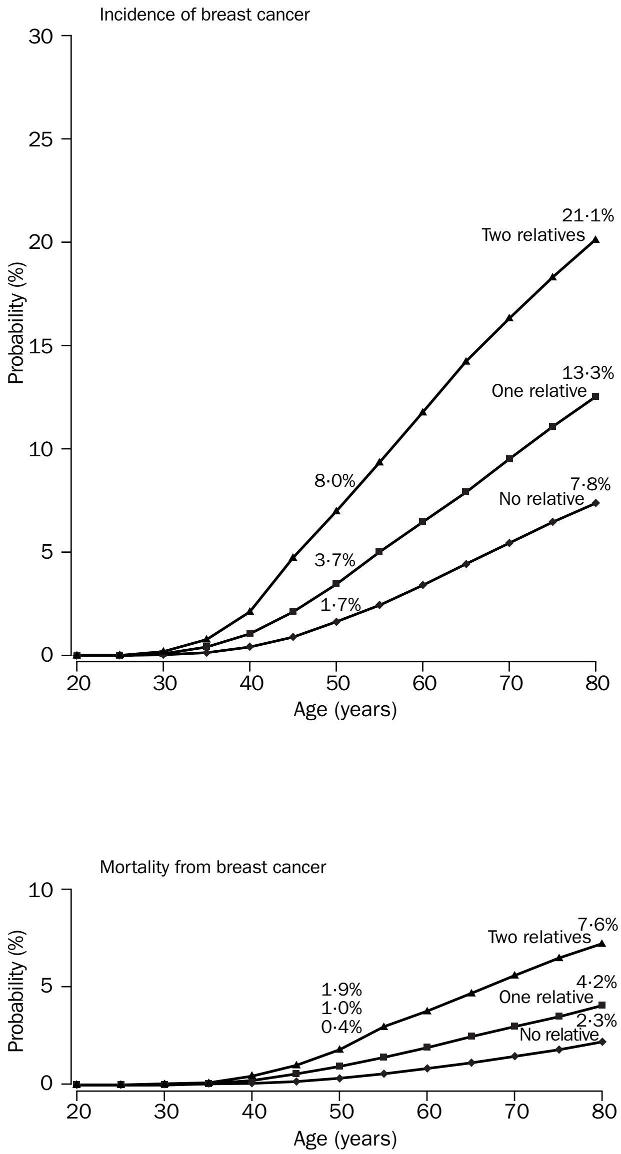


Figure 4: **Probability (%) that women in more-developed countries who are free from breast cancer at age 20 will develop the disease (incidence) or die from it (mortality) by various ages, according to the number of affected relatives**
See methods.

Age (years)	Number of first-degree relatives now affected		
	Two	One	None
% of women in each family history category with breast cancer/without breast cancer			
20–29 (=100%)	0·8/0·06	8·8/2·5	90/97
30–39 (=100%)	0·9/0·1	10·2/4·6	89/95
40–49 (=100%)	0·9/0·3	11·7/6·3	87/93
50–59 (=100%)	1·2/0·5	12·9/8·1	86/91
60–69 (=100%)	1·7/0·7	13·0/8·4	85/91
70–79 (=100%)	2·3/0·9	13·9/8·5	84/91
Overall (=100%)	1·3/0·5	12·2/7·3	87/92

Table 7: **Distribution of women with and without breast cancer in studies from more-developed countries, according to their age and family history of breast cancer**

developing breast cancer from age 20 to 80 were 16·1% and 12·3%, respectively, for women whose relative was younger than 40, and 60 or older, at diagnosis. This finding indicates that the excess lifetime incidence of breast cancer for women with one relative affected before age 40 compared with over age 60 is 3·8%. For women with more than one affected relative, the data are insufficient to permit reliable re-estimation of incidence, taking into account their relatives' ages.

Mortality from breast cancer

These results suggest little or no difference in the extent of spread of the breast cancer in women with and without a family history of the disease. On the assumption that, for a given tumour stage, survival is similar in women with and without affected first-degree relatives, the risk ratios for incidence estimated here were used to estimate risk ratios for mortality (lagged by 10 years to allow for the time between diagnosis and death). Figure 4 shows the estimated cumulative mortality from breast cancer from age 20 to 80, according to the number of affected first-degree relatives. The lifetime risk of death from breast cancer was estimated to be 2·3%, 4·2%, and 7·6%, respectively, for women with zero, one, and two affected relatives.

Proportion of the population with familial breast cancer

Table 7 shows age-specific data on the proportions of women with breast cancer and without breast cancer (ie, controls) in more-developed countries who have zero, one, or two or more first-degree relatives with a history of breast cancer. Since the large majority of studies contributing to this collaboration are population-based,[2] the data in table 7 are likely to be broadly representative of the general population in the countries where the studies were done. In each age-group, 90% or more of the women without breast cancer did not have an affected first-degree relative. Furthermore, the proportion of women without breast cancer who had one or more affected first-degree relatives increased with age, from 3% at age 20–29 to 9% at age 70–79. At each age, 1% or fewer women without breast cancer had two or more affected relatives; since only 0·04% had three or more affected relatives, the 1% comprises, almost entirely, women with exactly two affected relatives.

Among women in more-developed countries with incident breast cancer, the large majority (90% at age 20–29, 84% at age 70–79) reported that they did not have any affected first-degree relative (table 7). Overall in these studies 87% of breast cancers occurred in women with no affected first-degree relatives, 12% in women with one affected relative, and 1% in women with two or more affected relatives. The proportion of controls reporting a history of breast cancer in first-degree relatives was substantially lower in less-developed than in more-developed countries (2% *vs* 8%). The incidence of breast cancer is lower in less-developed than in more-developed countries and estimates of absolute risk would be substantially lower in less-developed countries than those quoted for more-developed countries.

Discussion

This collaborative reanalysis of individual data from 52 studies confirms the well-established increased risk of breast cancer among women with a family history of the disease. It also shows, however, that most women with one or more affected first-degree relatives will never develop the disease themselves and that most women who develop breast cancer do not have an affected first-degree relative.

Bias and confounding

Women included in these analyses were recruited independently of their family history of breast cancer. Moreover, since the selection of controls from studies in more-developed countries are largely population-based the prevalences of various patterns of breast cancer in their first-degree female relatives can be taken to be representative of those countries. Hence, the risk ratios and estimates of absolute risk presented here are largely population-based and unlikely to be unduly influenced by selective ascertainment, which often biases estimates derived from analyses of family pedigrees.

Information about breast cancer in first-degree relatives was self-reported, and women who already had breast cancer may have been likely to report the disease in their relatives more completely than were women without breast cancer. This type of differential reporting should not bias results from cohort studies, since family history data are reported before women are diagnosed with breast cancer. The results from cohort studies were, however, similar to the overall results.

Another possible bias is increased surveillance, with the earlier detection of breast cancer among women with a family history of the disease. If so, the breast cancers diagnosed in women with a family history would be expected to be less advanced clinically than those diagnosed in women without a family history. The results show, however, little difference in the extent of disease spread between women with and without a family history.

Women with breast cancer reported fewer children and fewer sisters than women without breast cancer. The smaller number of children among cases is expected, because the risk of breast cancer is reduced by childbearing (figure 2), and the smaller number of sisters among cases is because the tendency for small families runs in families (among controls aged more than 45, who would have completed their childbearing, the average number of children a woman had increased progressively with her number of sisters; the average parity being 2·5, 2·6, 2·7, 2·8, 3·0, and 3·1, respectively, for women with zero, one, two, three, four, and five or more sisters). However, stratification of all analyses by each woman's parity and number of sisters kept confounding due to these factors to a minimum.

The fine stratification used in these analyses means that no direct comparisons were made between women in one study and women in another and that the family history of women with breast cancer was compared only with that of control women who were of exactly the same age, who had similar reproductive histories, and who had a similar number of sisters. Although the stratification was fine enough to avoid any substantial confounding by these factors, it was not excessively fine, since much of the statistical information content remained after the stratification (see web table on *The Lancet*'s website: www.thelancet.com). Additional adjustment for other potential confounding factors, such as age at menarche, years of education, height, and weight, was found not to affect the main results greatly.

Potential interaction with other factors

The analyses shown in figure 3 were done to investigate whether various factors, many of which are known to affect the risk of developing breast cancer, modify the risk ratios associated with a family history of the disease. Altogether 12 factors were examined in two separate age-groups and overall there was no strong evidence of an interaction between the effects of family history and the other factors, in terms of the relative risk of breast cancer.

The results in figure 2 show that, among women with one or more affected first-degree relatives, there were independent effects of other factors such as parity, the age at which a woman's first child was born, and menopause, which were similar to those seen in women without affected relatives (web figure 1) and in the study population as a whole.[1–3] However, even in this large dataset, the results for women with affected first-degree relatives who had used oral contraceptives or hormone-replacement therapy were based on comparatively small numbers. Within the limits of the available data there is, nevertheless, little evidence to suggest an adverse interaction between use of such hormonal therapies and having first-degree relatives with a history of breast cancer with respect to the relative risk of developing the disease.

Although the proportional effects of reproductive factors did not differ in women according to family history, these factors would have different effects on the absolute magnitude of disease—ie, on incidence and mortality rates for breast cancer, in women with and without affected relatives. For example, reproductive factors that reduce the risk ratio for breast cancer, such as high parity, early childbearing, and early menopause, should lead to a greater reduction in the absolute incidence of breast cancer in women with family history of the disease than in women without such a history, just because the relevant risk ratios are similar in both groups.

Limitations of the data

The data analysed here relate solely to the risk of breast cancer associated with a history of breast cancer in first-degree female relatives. No data were sought on a history of breast cancer in other relatives, on whether women had mutations of the *BRCA*1 and *BRCA*2 genes, or about a family history of other cancers. Furthermore, the analyses could not take account of attained ages of all first-degree relatives at the time when information was collected, since few studies recorded such details. Although the data analysed here are of limited value in assessing the role of genetic factors in breast cancer, the indices of familial breast cancer examined, such as the number of affected first-degree relatives and their ages at diagnosis of breast cancer, are commonly used in counselling of women.

All studies provided information on breast cancer in mothers and sisters of cases and controls, but only 17 provided information about daughters. Few of those daughters had a history of breast cancer, largely because the women included in these analyses were themselves, on average, aged just over 50 (table 1), so their daughters would still be too young to have developed the disease. Thus, separate analyses of the risk of a mother developing breast cancer, given that her daughter was affected, were not possible. This risk ratio should, in principle, be similar to that of a daughter developing the disease, given that her mother was affected; and many of the data analysed here pertain to such a situation.

Among the 58 209 women with breast cancer included in these analyses, only 603 (1·0%) had exactly two affected first-degree relatives and 83 (0·1%) had three or more affected relatives. These proportions reflect the comparative rarity of multiple cases of breast cancer in first-degree relatives of women in more-developed countries, which, in turn, is associated with the small family sizes of women in these countries. Thus, the data contributed to this collaboration are of limited value for studying extremely rare familial clusters of breast cancer or the mode of inheritance of genes that affect susceptibility to breast cancer.

The estimates of the probability of developing or dying from breast cancer up to a certain age are based on breast cancer incidence and mortality rates that were prevalent in more-developed countries around 1990 and assume that the age-specific risk ratios shown in figure 1 apply directly for incidence and 10 years later for mortality. The estimates also take into account the fact that, as women age, a certain proportion of their relatives will be diagnosed with breast cancer. In some countries, breast-cancer incidence rates have increased since 1990, often in association with the increasing use of mammographic screening, and death rates have fallen. Because of the various assumptions made and the changing pattern of breast cancer in many countries, the figures quoted here should be taken as broadly indicative of breast-cancer rates for women currently living in more-developed countries. If national breast-cancer incidence and mortality rates continue to change substantially, recalculation of these estimates may be necessary.

Dual effect of the woman's and her relative's age

For a woman who already has one or more affected first-degree relatives, her risk of developing breast cancer depends both on her own age and on the ages her relatives were when they developed breast cancer. Individual studies have not been large enough to characterise reliably this dual dependence on age. The risk ratios shown in tables 3 and 4 provide such estimates for women with exactly one and exactly two affected first-degree relatives. As would be expected, the risk ratios tended to be higher for younger women, and, for a fixed age of the proband, the risk ratios were higher the younger the relative was when her breast cancer was diagnosed. The largest risk ratios are therefore found when the women and their relatives were aged less than 50.

It might be expected that, for women with one affected first-degree relative, the corresponding rate ratios above and below the diagonal in table 3 would be similar. For example, the relevance for a woman aged less than 40 of having one relative affected at age 50–59 would be expected to be the same as for a woman aged 50–59 having one relative affected at age less than 40. However, the risk ratios above the diagonal tended to be somewhat greater than the corresponding ratios below the diagonal. Such asymmetry persisted when results were examined separately for affected mothers and sisters (data not shown).

Breast cancer is uncommon at young ages and the larger risk ratios found for young women with a family history of the disease have comparatively small effects on the absolute lifetime incidence of and mortality from breast cancer.

Implication for counselling women and for public health

Overall, the estimated lifetime incidence of breast cancer for women in more-developed countries—ie, the probability of developing breast cancer between ages 20 and 80—is 7·8% (one in 13 women) with no affected first-degree relative, 13·3% (one in eight) with one affected relative, and 21·1% (one in five) with two affected relatives. Corresponding estimates for lifetime mortality are 2·3% (one in 43), 4·2% (one in 24), and 7·6% (one in 13). A history of breast cancer in three or more first-degree relatives is extremely rare, and the corresponding estimated lifetime cumulative incidence of breast cancer is about 30%.

These results have important implications both for counselling of women and for public-health practitioners. First, most women with one or more affected first-degree relatives are themselves unlikely to develop breast cancer and even less likely to die from it. For example, for women in more-developed countries with two affected first-degree relatives, about four-fifths would never be diagnosed with breast cancer and 12 of 13 would not die from breast cancer.

Second, if women with a family history of breast cancer do develop the disease, their breast cancer is most likely to be diagnosed in middle or old age. For example, the excess incidence after age 50 is 3·7% for women with one affected relative and 8·6% for women with two, compared with excesses of 2·0% and 6·3%, respectively, before age 50. Thus, even though the risk ratio of breast cancer is greatest at young ages, the absolute incidence of breast cancer is not.

Third, for women with a given number of affected relatives, the ages the relatives were when their cancers were diagnosed have only a moderate effect on the lifetime risk of developing breast cancer. This is because the relatives' ages are relevant mainly for breast cancers that occur at young ages, when the incidence of breast cancer is low.

Fourth, the large majority of women who develop breast cancer have no mother, sister, or daughter with a history of the disease. In more-developed countries, eight out of nine breast cancers occur in women with no history of breast cancer in a first-degree relative. The proportion with affected relatives is slightly less at young ages and is likely to be less still among women in less-developed countries. Thus, any public-health programme aimed solely at the early detection of breast cancer in women with affected first-degree relatives would, at all ages and in all countries, miss the large majority of women who develop the disease.

Analysis and Writing Committee

Valerie Beral, Diana Bull, Richard Doll, Richard Peto, and Gillian Reeves.

Steering committee

David Skegg (chairman) Graham Colditz, Barbara Hulka, Carlo La Vecchia, Cecelia Magnusson, Tony Miller, Bert Peterson, Malcolm Pike, Matti Rookus, David Thomas.

Acknowledgments

This review would not have been possible without the tens of thousands of women with and without breast cancer who took part in this research. The carefully collected data provided by each of the collaborating institutions contributed substantially to the quality of the overall results. Central pooling, checking, and analysis of data were supported by the Imperial Cancer Research Fund and the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction.

References

1 Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet* 1996; **347:** 1713–27.

2 Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: further results. *Contraception* 1996; **54** (suppl 3)**:** 1S-106S.

3 Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. *Lancet* 1997; **350:** 1047–59.

4 Vessey M, Baron J, Doll R, McPherson K, Yeates D. Oral contraceptives and breast cancer: final report of an epidemiologic study. *Br J Cancer* 1983; **47:** 455–62.

5 Lê MG, Bachelot A, Doyon F, Kramar A, Hill C. Oral contraceptive use and breast cancer or cervical cancer: preliminary results of a French case-control study. In: Wolff OP, Scott JS, eds. Hormones and sexual factors in human cancer aetiology. Amsterdam: Elsevier Science Publishers, 1984: 139–47

6 Hislop TG, Coldman AJ, Elwood JM, Brauer G, Kan L. Childhood and recent eating patterns and risk of breast cancer. *Cancer Detect Prev* 1986; **9:** 47–58.

7 Meirik O, Lund E, Adami HO, Bergstrom R, Christoffersen T, Bergsjo P. Oral contraceptive use and breast cancer in young women: a joint national case-control study in Sweden and Norway. *Lancet* 1986; **2:** 650–54.

8 Nomura AMY, Kolonel LN, Hirohata T, Lee J. The association of replacement estrogens with breast cancer. *Int J Cancer* 1986; **37:** 49–53.

9 Lubin F, Wax Y, Modan B. Role of fat, animal protein and dietary fibre in breast cancer aetiology: a case-control study. *J Natl Cancer Inst* 1986; **77:** 605–12.

10 Alexander FE, Roberts MM, Huggins A. Risk factors for breast cancer with applications to selection for the prevelance screen. *J Epidemiol Community Health* 1987; **41:** 101–06.

11 Lee NC, Rosero-Bixby L, Oberle MW, Grimaldo C, Whately AS, Rovira EZ. A case-control study of breast cancer and hormonal contraception in Costa Rica. *J Natl Cancer Inst* 1987; **79:** 1247–54.

12 Ravnihar B, Primic Zakelj M, Kosmelj K, Stare J. A case-control study of breast cancer in relation to oral contraceptive use in Slovenia. *Neoplasma* 1988; **35:** 109–21.

13 Rohan TE, McMichael AJ. Oral contraceptive agents and breast cancer: a population-based case-control study. *Med J Aust* 1988; **149:** 520–26.

14 Yuan J-M, Yu MC, Ross RK, Gao Y-T, Henderson BE. Risk factors for breast cancer in Chinese women in Shanghai. *Cancer Res* 1988: **48:** 1949–53.

15 Romieu I, Willett W, Colditz G, et al. Prospective study of oral contraceptive use and the risk of breast cancer in women. *J Natl Cancer Inst* 1989; **81:** 1313–21.

16 Siskind V, Schofield F, Rice D, Bain C. Breast cancer and breast feeding: results from an Australian case-control study. *Am J Epidemiol* 1989; **130:** 229–36.

17 Stanford JL, Brinton LA, Hoover RN. Oral contraceptives and breast cancer: results from an expanded case-control study. *Br J Cancer* 1989; **60:** 375–81.

18 UK National Case-Control Study Group. Oral contraceptive use and breast cancer risk in young women. *Lancet* 1989; **1:** 973–82.

19 McPherson K, Vessey MP, Neil A, Doll R, Jones L, Roberts M. Early oral contraceptive use and breast cancer: results of another case-control study. *Br J Cancer* 1987; **56:** 653–60.

20 Paul C, Skegg DCG, Spears GFS. Oral contraceptives and risk of breast cancer. *Int J Cancer* 1990; **46:** 366–73.

21 Schildkraut JM, Hulka BS, Wilkinson WE. Oral contraceptives and breast cancer: a case-control study with hospital and community controls. *Obstet Gynecol* 1990; **76:** 395–402.

22 Clavel F, Andrieu N, Gairard B, et al. Oral contraceptives and breast cancer: a French case-control study. *Int J Epidemiol* 1991; **20:** 32–38.

23 Gajalakshmi CK, Shanta V. Risk factors for female breast cancer: a hospital based case-control study in Madras, India. *Acta Oncol* 1991; **30:** 569–74.

24 Segala C, Gerber M, Richardson S. The pattern of risk factors for breast cancer in a Southern France population: interest for a stratified analysis by age at diagnosis. *Br J Cancer* 1991; **64:** 919–25.

25 Weinstein AL, Mahoney MC, Nasca PC, Leske MC, Varma AO. Breast cancer risk and oral contraceptive use: results from a large case-control study. *Epidemiology* 1991; **2:** 353–58.

26 Wingo PA, Lee NC, Ory HW, Beral V, Peterson HB, Rhodes P. Age-specific differences in the relationship between oral contraceptive use and breast cancer. *Obstet Gynecol* 1991; **78:** 161–70.

27 Lee HP, Gourley L, Duffy SW, Esteve J, Lee J, Day NE. Risk factors for breast cancer by age and menopausal status: a case-control study in Singapore. *Cancer Causes Control* 1992; **3:** 313–22.

28 Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study, I: breast cancer detection and death rates among women aged 40–49 years. *Can Med Assoc J* 1992; **147:** 1459–76.

29 Rosenberg L, Palmer JR, Clarke EA, Shapiro S. A case-control study of

the risk of breast cancer in relation to oral contraceptive use. *Am J Epidemiol* 1992; **136:** 1437–44.

30 Sellers TA, Kushi LH, Potter JD, et al. Effect of family history, body fat distribution, and reproductive factors on risk of postmenopausal breast cancer. *N Engl J Med* 1992; **326:** 1323–29.

31 Wang Q-S, Ross RK, Yu MC, Ning J-P, Henderson BE, Kimm HT. A case-control study of breast cancer in Tianjin, China. *Cancer Epidemiol Biomarkers Prev* 1992; **1:** 435–39.

32 Yang CP, Daling JR, Band PR, Gallagher RP, White E, Weiss NS. Non contraceptive hormone use and risk of breast cancer. *Cancer Causes Control* 1992; **3:** 475–79.

33 Calle EE, Martin LM, Thun MJ, Miracle HL, Heath CW Jr. Family history, age, and risk of fatal breast cancer. *Am J Epidemiol* 1993; **138:** 675–81.

34 Kalache A, Maguire A, Thompson SG. Age at last full-term pregnancy and risk of breast cancer. *Lancet* 1993; **341:** 33–36.

35 Tavani A, Negri E, Franceschi S, Parazzini F, La Vecchia C. Oral contraceptives and breast cancer in Northern Italy: final report from a case-control study. *Br J Cancer* 1993; **68:** 568–71.

36 Newcomb PA, Storer BE, Longnecker MP, et al. Lactation and a reduced risk of premenopausal breast cancer. *N Engl J Med* 1994; **330:** 81–87.

37 Ngelangel CA, Lacaya LB, Cordero C, Laudico AV. Risk factors for breast cancer among Filipino women. *Philipino J Intern Med* 1994; **32:** 231–36.

38 Rookus MA, van Leeuwen FE, for the Netherlands Oral Contraceptives and Breast Cancer Study Group. Oral contraceptives and risk of breast cancer in women aged 20–54 years. *Lancet* 1994; **344:** 844–51.

39 Schairer C, Byrne C, Keyl PM, Brinton LA, Sturgeon SR, Hoover RN. Menopausal estrogen and estrogen-progestin replacement therapy and risk of breast cancer (United States). *Cancer Causes Control* 1994; **5:** 491–500.

40 White E, Malone KE, Weiss NS, Daling JR. Breast cancer among young US women in relation to oral contraceptive use. *J Natl Cancer Inst* 1994; **86:** 505–14.

41 Brinton LA, Daling JR, Liff JM, et al. Oral contraceptives and breast cancer risk among younger women. *J Natl Cancer Inst* 1995; **87:** 827–35.

42 La Vecchia C, Negri E, Franceschi S, et al. Oral contraceptives and breast cancer: a cooperative Italian study. *Int J Cancer* 1995; **60:** 163–67.

43 Lipworth L, Katsouyanni K, Stuver S, Samoli E, Hankinson SE, Trichopoulos D. Oral contraceptives, menopausal estrogens, and the risk of breast cancer: a case-control study in Greece. *Int J Cancer* 1995; **62:** 548–51.

44 Primic-Zakelj M, Evstifeeva T, Ravnihar B, Boyle P. Breast cancer risk and oral contraceptive use in Slovenian women aged 25 to 54. *Int J Cancer* 1995; **62:** 414–20.

45 Schuurman AG, van den Brandt PA, Goldbohm RA. Exogenous hormones and the risk of postmenopausal breast cancer: results from the Netherlands cohort study. *Cancer Causes Control* 1995; **6:** 416–24.

46 Levi F, Pasche C, Lucchini F, La Vecchia C. Alcohol and breast cancer in the Swiss Canton of Vaud. *Eur J Cancer* 1996; **32A:** 2108–13.

47 Rossing MA, Stanford JL, Weiss NS, Habel LA. Oral contraceptive use and risk of breast cancer in middle-aged women. *Am J Epidemiol* 1996; **144:** 161–64.

48 Viladiu P, Izquierdo A, de Sanjose S, Bosch FX. A breast case-control study in Girona, Spain. Endocrine, familial and lifestyle factors. *Eur J Cancer* 1996; **5:** 329–35.

49 McCredie MRE, Dite GS, Giles GG, Hopper JL. Breast cancer in Australian women under the age 40. *Cancer Causes Control* 1998; **9:** 189–98.

50 Hirose K, Tajima K, Hamajima N, et al. Comparative case-referent study of risk factors among hormone-related female cancers in Japan. *Jpn J Cancer Res* 1999; **90:** 255–61.

51 Hopper JL, Chenevix-Trench G, Jolley D, et al. Design and analysis issues in a population-based case-control-family study of the genetic epidemiology of breast cancer, and the Cooperative Family Registry for Breast Cancer Families (CFRBCS). *Monogr Natl Cancer Inst* 1999; **26:** 95–100.

52 Magnusson C, Baron JA, Correia N, Bergstrom R, Adami H-O, Persson I. Breast cancer risk following long-term oestrogen- and oestrogen-progestin-replacement therapy. *Int J Cancer* 1999; **81:** 339–44.

53 Million Women Study Collaborative Group. The Million Women Study: design and characteristics of the study population. *Breast Cancer Res* 1999; **1:** 73–80.

54 Easton DF, Peto J, Babiker AGAG. Floating absolute risk: an alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. *Stat Med* 1991; **10:** 1025–35.

55 Peto R, Lopez AD, Boreham J, Thun M, Heath C. Mortality from smoking in developed countries 1950–2000. Oxford: Oxford University Press, 1995.